accordance with the Examiner's suggestions, the enclosed Abstract is the same as PCT/FR97/00334.

As to the Information Disclosure Statement and translations, the Applicants are submitting herewith in a supplemental IDS translations of the following:

a. USPTO Serial No. 081383,322, filed January 30, 1995 which is the U.S. version of WO94 22462 (Torossion);

b. U.S. Patent No. 4,460,575 which is the U.S. case corresponding to EPO 035 429 (Fabre); and

c. Article: Use of Bacterial Ribosomal Immunostimulators in Respiratory Tract Infections" (Clinical Immunotherapics, vol. 4, no. 2, 1995 – Faure et al).

In the claims, the original set of claims 1-8 have been withdrawn and a new set of claims 9-16 substituted therefore. The new claims correspond to the subject matter of the withdrawn claims, but the new claims have been presented with the Examiner's comments in mind and have been revised to overcome all of the objections. Also, in view of the above changes to the Specification and comments contained below, it is submitted that the subject matter of all of the claims is fully supported by the Specification.

In the Specification, appropriate headings have been inserted where necessary in order to place the application in the proper format or arrangement. Also, several misspellings have been corrected, the names of

bacterial species have been italicized, and the citations to several of the references have been completed. No new matter has been added. It is now believed that the Specification is in proper form and that all of the Examiner's objections to it have been overcome.

Original claims 1-8 were rejected under 35 U.S.C. §112, first paragraph, as failing to provide an adequate written description and as failing to provide an enabling disclosure. That ground for rejection is respectfully traversed for the reasons stated below. Also, claims 1-8 were rejected under 35 U.S.C. §112, second paragraph, as being indefinite for various reasons. As to the latter ground for rejection, the revised new set of claims 9-16 have been drafted with the Examiner's comments in mind and are believed to be in full compliance with §112. It is submitted that all of the Examiner's specific objections to the claims have been overcome.

It is submitted that the claims of the present application are sufficient to allow persons skilled in the art to make and use the invention. The claims contain subject matter which is either described in the Specification or evident to persons of ordinary skill in the art.

1) **Therapeutic, preventive, vaccinal, immunomudulator complex:**

The complex of the invention is composed of two major components which provide double action of the complex as explained in the patent application (see page 1, lines 1 to 7):

(a) a specific action against *Helicobecter* (former *Campylobacter*) by means of RNA of ribisomal origine extracted specifically form the bacteria of claim 1;

(b) a non-specific action by the means of non-specific antigens providing immunomodulation.

The specificity is clearly directed to *Helicobacter* species (page 1, line 4: "specific antigens against *Helicobacter pylori, Helicobacter hepaticus, Helicobacter coronari.*").

It is a therapeutic and vaccinal complex according to the application page 1, lines 1-3:

> "The present invention relates to a therapeutic and preventive vaccine complex..."

The double effect of vaccination, that is both therapeutic and preventive, is well known to persons skilled in the art as is demonstrated by the definition of "vaccine" in Dorland's Medical Dictionary, page 1787 (28th ed.) (Exhibit A attached hereto):

> "Vaccine: suspension of attenuated or killed micro-organisms or of antigenic proteins derived from them, administrated for the prevention, amelioration or treatment of infectious diseases."

The expressions "therapeutic complex" and "vaccine complex" are used with the same meaning.

The wording of the claims has been changed to make them more consistent with each other. In this regard, the therapeutic immunomodular complex of original claim 1 (now claim 9) and the anti-*Helicobacter*-

specific immunomodulator and vaccine complex of original claim 7 (now claim 15) are the same. The claims have been revised to clarify this.

2) Functional arm and genetic arm

The "functional amino-acid arm, with a genetic RNA arm corresponding to the coded description of the composition of the functional arm" has been defined in the Scientific American by Gerald Joyce. The relevant part from the French version "Pour la Science," No 184, February 1993, page 77 (attached hereto as Exhibit B) is translated as follows:

> "S. Brenner and R. Lerner prepared molecules, so called dual molecules, composed of two "arms" joined in one point. The first arm is a functional macro-molecule which capacity to bind to a target is checked. It is constituted to amino-acids, sugar or any organic sub-unit. The second arm is a genetic macromolecule, that contains a coded description of the functional arm: its nucleotidic sequence describes the functional arm sub-units.

This data was published in a journal aimed to a large public and is therefore included in the technological background of persons skilled in the art.

The method used in the invention is a method of genetic amplication close to PCR (Polymerase Chain Amplification) which uses a mechanism of the directed molecular evolution, based upon putting in contact ribosomal RNA fragments with specific amino-acids. According to the directed molecular evolution model, amino-acids arrange themselves on the ribosomal RNA fragments and reconstitute fractions of immunogenic ribosomal proteins giving a duplication of immunological sites.

The Youmans works gave a large contribution for showing the part of the ribosomal fractions in the specific and non-specific mechanisms of immunity. Fractions of ribosomal proteins alone or bound to membranal fractions give immunostimulant complexes which have the property to stimulate the activity of the immune system and to reinforce the system's defense means. (See Youmans, page 15 of the application).

3) Anti-idiotype vaccine

The Dorland Medical Dictionary, page 818 of the 28th edition (Exhibit A), gives the definition of an idiotype:

> "A set of one or more idiotopes that distinguish a clone from other clones."

In Immunointervention in Man, Oxford Medical Publications, 1991, page 13 (Exhibit C), it is explained that:

> "when an antibody interacts with a foreign antigen, it binds to a surface configuration of that antigen, referred to as an 'epitope,' by means of a complementary structure or shape in its antigen-binding region. This structure on the antibody molecule is actually a unique structure within the body and is called the idiotype of that antibody. This generates an immune response, giving rise to another antibody (anti-antibody or anti-idiotype) that combines with it... . Anti-idiotype can bind with cell-bound antigen receptor molecule and limit their proliferation and further differentiation.

Thus, these structures and their uses as anti-idiotypic vaccines are elements of the available technical knowledge. The ability "to limit the proliferation and further differentiation" is the evident reason why their use "makes it possible to avoid recidivations of the initial digestive tract

pathology" as claimed in claim 5 (now claim 13). The technical background of persons skilled in the art includes all of this data.

In view of the foregoing explanation, it is submitted that the claims are adequately supported by the express language of the Specification as supplemented by knowledge available to and/or known by persons of ordinary skill in the art. As a result, the rejection of the claim under §112, first paragraph, should be withdrawn.

With the above explanations in mind, and with the revised set of new claims 9-16 in view, virtually all of the Examiner's comments on, and §112 objections to, the claims in Paragraph 13 of the Office Action have been overcome or obviated. As to some of the comments and objections in particular, the following comments and responses are submitted:

a. Paragraph 13(b) – The coupling is a covalent binding, as set forth in the Specification (p. 2, line 4). Indeed, a duel molecule is a single molecule constituted of two parts that can play a distinct role. These parts are compared to arms that are joined at one point.

b. Page 13(i) – In claim 4 (now claim 12), the diseases caused by *Helicobacter* bacteria are those that are described on page 3, line 9 to page 4, line 8 of the application. In particular the pathologies can be adenocarcinoma, gastric lymphoma or mucous associated lymphoid tissue lymphomas (page 3, lines

16-18). The *Helicobacter* species are those of claim 9, since claim 12 depends on claim 9. The Specification provides full information about *H. pylori* (page 3, line 19 to page 4, line 8), and about *Campylobacter jejuni* (page 4, lines 5-8). Persons skilled in the art know that humans are the only host of these bacteria. Concerning the question of the production of antibodies against antigenic components of *Helicobacter* species, it can be referred to the mechanism of action described on page 14, line 23 to page 19, line 18. In particular, the complex induces the production of antibodies against the site for attachment of the bacteria (page 17, lines 1-3). This action is also accompanied by production of endogenous interferon (page 17, lines 9-10). The production of antibodies is the result of the action of the complex as a vaccine, and the production of endogenous interferon is the result of the action of the complex as an immunomodulator.

c. Paragraph 13(o) – As explained above, there is no difference between the immunomodulatory complex and the vaccine complex, because the complex of the invention provides both effects at the same time. The claims have been amended accordingly.

d. Paragraph 13(b) – The complex of claim 9 contains two types of elements, i.e., bacterial membrane fractions and ribosomal RNA originating from defined bacteria. The two types of elements induce immunological responses that are directed against the different micro-organisms from which the antigenic elements were selected to prepare the complex. The association of multiple immunological stimulating elements is a reason for the success of the complex to avoid recidivations of the initial pathology. Claim 13 includes material from all the bacteria of claim 9.

e. Paragraph 13(t) – The therapeutic mechanism makes it possible to produce a natural cloning (page 16, lines 25-26) that induces vaccination (page 17, line 1), and is accompanied by production of endogenous interferon (page 17, line 10). From the Specification, it is clear that in new claim 12, the production of interferon takes place in the host, by the mean of a natural cloning. All the elements of claim 9 induce immunological responses that are directed against the different micro-organisms from which the antigenic elements were selected to prepare the complex.

f. Paragraph 13(w) – In claim 15, the factors linked to the bacterium and the factors linked to the host are well known

since the administration of a vaccine induces inflammatory reactions that are related (linked) to the secretion of substances by the bacterium, for example cytotoxins, or to the response of the immune system of the patient (host). "Packaging" has been changed to the correct word "formulation." The word "administration" in this context means the application or introduction of a therapeutic substance to a patient. A "packaging allowing the simultaneous administration" is understood to mean "a formulation enabling the simultaneous administration of the said complex and of major... ."

In view of the foregoing, it is submitted that all of the claims remaining in the case, namely claims 9-16, fully met the standards of 35 U.S.C. §112 and patentably distinguish from the prior art. Accordingly, allowance of the claims and passage of the application to issuance are respectfully requested.

Respectfully submitted,

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ABSTRACT

A therapeutical vaccine complex having activity specific for *Helicobacter* bacteria as well as non-specific immunomodulation activity for regulating the natural defenses of the body. The drug is also useful for preventing relapses, particularly in cases of resistance to conventional treatment. The drug essentially consists of RNA, selective membrane fractions of microbial germs, particular amino acid sequences, sodium chloride and a steroidal anti-inflammatory in predetermined proportions enabling simultaneous delivery of antibiotics and frenosecretories. Said drug is particularly suitable for treating digestive tract diseases caused by *Helicobacter* (antral gastritis, duodenal ulcers, gastric ulcers, oesophagitis, hepatitis) and preventing stomach cancer and degenerative infectious MALT (mucosa-associated lymphoid tissue) lymphoma, as well as coronary diseases directly or indirectly dependent on *Helicobacter* infections.